Complete Summary

GUIDELINE TITLE

The treatment of locally advanced pancreatic cancer.

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Earle CC, Agboola O, Maroun J, Zuraw L. The treatment of locally advanced pancreatic cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Feb 20 [online update]. 17 p. (Practice guideline report; no. 2-7). [29 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Locally advanced (unresectable but non-metastatic) pancreatic cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the optimal treatment for patients with locally advanced (unresectable but non-metastatic) pancreatic cancer

TARGET POPULATION

Adult patients with locally advanced (unresectable but nonmetastatic) adenocarcinoma of the exocrine pancreas

INTERVENTIONS AND PRACTICES CONSIDERED

1. Chemoradiotherapy (bolus 5-fluorouracil [5-FU] combined with radiation)
2. Radiotherapy alone
3. Chemotherapy alone
4. Anti-cancer treatments (listed above) in combination with supportive care (e.g., pain control, nutritional support)

Note: Guideline developers considered but did not recommend supportive care alone in patients medically suitable for chemotherapy and radiation treatment.

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease-free survival
- Local control
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original Guideline

MEDLINE (1966 to March [week 3] 2002), CANCERLIT (1983 to October 2001), and the Cochrane Library (2002, Issue 1) were searched with no language restrictions. "Pancreatic neoplasms" (Medical Subject Heading [MeSH]) was combined with "chemotherapy, adjuvant" (MeSH), "radiotherapy" (MeSH), "immunotherapy" (MeSH), and each of the following phrases used as text words: "chemotherapy," "radiotherapy," "radiation," "immunotherapy." These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/cancerinfo/pdq/) and the proceedings of the 1996–2001

annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999–2001 annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by each reviewer independently, and the reference lists from these sources were searched for additional trials.

2004 Update

The original literature search was updated in February 2004 using the MEDLINE (March 2002 to February week 1 2004), EMBASE (1996 through 2004, week 6), and Cochrane Library databases (to Issue 3, 2003), along with abstracts from the 2003 proceedings of the annual meetings of American Society of Clinical Oncology and American Society for Therapeutic Radiology and Oncology. The PDQ database was also searched for relevant ongoing trials. Due to a decision in April 2003 by the U.S. National Library of Medicine to no longer update the CANCERLIT database, as of May 2003, the CANCERLIT database will no longer be searched when updating.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of randomized trials and meta-analyses comparing combinations of chemotherapy, radiotherapy, and/or immunotherapy to each other or supportive care alone in patients with locally advanced pancreatic cancer. Data on overall survival for patients with locally advanced pancreatic cancer had to be reported. Other outcomes of interest were disease-free survival, local control, adverse effects, and quality of life. If patients with metastatic disease were included in the study, results had to be reported separately for patients with locally advanced disease.

Exclusion Criteria

1. Phase I and II studies were not considered for inclusion in this report because of the availability of randomized trials.
2. Letters and editorials were not considered.

NUMBER OF SOURCE DOCUMENTS

22 randomized trials, one abstract report of a meta-analysis, and one preliminary repot of an ongoing trial were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Quantitative meta-analysis was not undertaken because the trials were too clinically heterogeneous to pool. The doses of radiotherapy varied widely, as did the chemotherapeutic agents and schedules.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Gastrointestinal Cancer Disease Site Group (DSG) reached fairly easy consensus on the guideline recommendations. Since the evidence for radiation is relatively weak, there was discussion around whether treatment with gemcitabine alone should be presented as an equally acceptable alternative. The only randomized data on gemcitabine is the study by Burris et al, which demonstrated that gemcitabine improves symptoms and modestly improves survival compared with 5-fluorouracil (FU) as single-agent chemotherapy in patients with locally advanced or metastatic pancreatic cancer. These patients were symptomatic, had a life expectancy of at least twelve weeks, and had a Karnofsky performance status of at least 50% (equivalent to an Eastern Cooperative Oncology Group [ECOG] performance status of less than 3). This randomized trial is discussed in detail in another guideline developed by the Gastrointestinal Cancer DSG, which concludes that gemcitabine is a reasonable treatment option in patients with locally advanced or metastatic pancreatic cancer. Since 26% of the patients included in the randomized trial by Burris et al had locally advanced disease (although they were not reported separately) and since the overall results detected a benefit with gemcitabine, the Gastrointestinal Cancer DSG inferred that patients with locally advanced disease unable to undergo radiation may be appropriately treated as having metastatic disease. A qualifying statement noting this was added to the recommendations.

The majority of Gastrointestinal Cancer DSG members felt that changing the phrase that states combined chemoradiotherapy is the "recommended standard" to "current conventional practice" was appropriate. Also, a qualifying statement that indicates to the reader that the evidence on which current conventional practice is based is modest at best was added to the recommendations. Based on feedback from the DSG members, some suggested chemotherapy regimens were added to the text of the document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 152 practitioners in Ontario (29 medical oncologists, 20 radiation oncologists, and 103 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gastrointestinal Cancer Disease Site Group (DSG) reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Ten of 11 members of the PGCC returned ballots. Eight members approved the practice guideline as written, and two members approved the guideline conditional on the Gastrointestinal Cancer DSG addressing specific concerns.

The practice guideline report was subsequently approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

2004 Update

Based on new evidence that was published after the original practice guideline was completed, the Gastrointestinal Cancer DSG decided to modify the qualifying statements. The updated qualifying statement was not distributed to practitioners, as the Gastrointestinal DSG considered the modification minor.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The intent of treatment of locally advanced pancreatic cancer is palliation in symptomatic patients and prolongation of life in medically suitable cases. The following options are appropriate:

- For medically suitable patients, current conventional practice is to offer combined chemotherapy and radiotherapy.
- Outside a clinical trial, 5-fluorouracil (5-FU) given as bolus or infusion is the preferred chemotherapeutic agent to combine with radiotherapy. The optimal

mode and duration of 5-fluorouracil delivery is unclear; however, infusional therapy appears to give better treatment outcome.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by evidence-based practice guidelines, meta-analyses, and randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Provision of optimal treatment for patients with locally advanced (unresectable but non-metastatic) pancreatic cancer with improved patient outcomes (e.g., overall survival, disease-free survival, local control, adverse effects and quality of life

POTENTIAL HARMS

Combination 5-fluorouracil (FU) and radiation is generally well tolerated; however, severe vomiting, mucositis, and leukopenia can occur in about 5% of patients. Although not superior to 5-fluorouracil in efficacy, other chemotherapeutic regimens appear to be more toxic.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Original Guideline

- Specific anti-cancer treatments (such as resection, chemotherapy, and radiation) may be supplemented with supportive care (such as pain control, nutritional support, biliary stenting, and bowel decompression as needed) if appropriate.
- The evidence on which current conventional practice is based is relatively weak.
- Chemotherapy alone with gemcitabine is an acceptable alternative.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

2004 Update

- Supportive care alone is not recommended in patients who are medically suitable for chemotherapy and radiation treatment.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Gastrointestinal Cancer Disease Site Group. Earle CC, Agboola O, Maroun J, Zuraw L. The treatment of locally advanced pancreatic cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Feb 20 [online update]. 17 p. (Practice guideline report; no. 2-7). [29 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 June 10 (revised 2004 Feb 20)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Gastrointestinal Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- The treatment of locally advanced pancreatic cancer. Summary. Toronto (ON): Cancer Care Ontario. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 25, 2004. This NGC summary was updated by ECRI on September 24, 2004. The updated information was verified by the guideline developer on October 20, 2004.

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